A Review of Healthy Sleep

To sleep, perchance to dream. . .

Topics

- Normal sleep
  - Sleep stages
  - Sleep cycles
- Sleep-wake Disorders
- RX:Sedative – Hypnotics
- TX: Psychoed, CBT

Normal Sleep

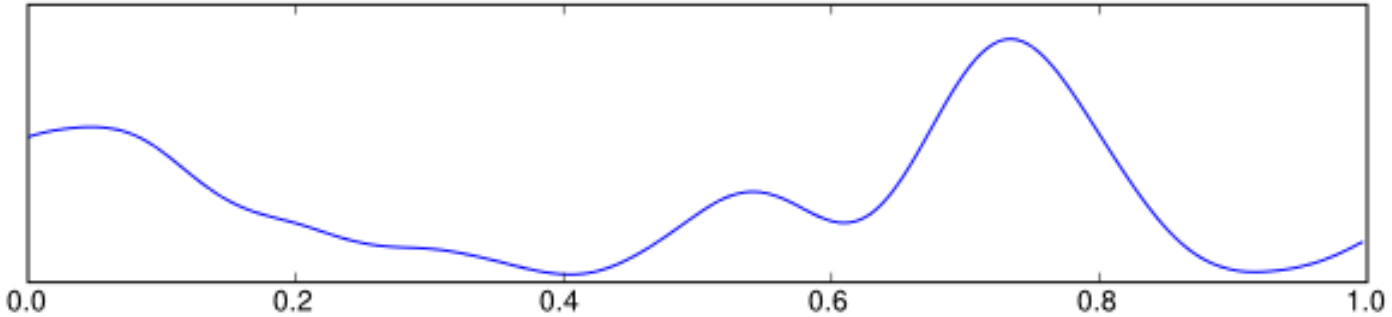
- **Stage 1**
  - Transition to sleep/slow eye movements
  - Alpha→Theta on EEG
  - Dreaminess, beginning to fall asleep
  - Hypnogogic hallucinations
  - Approx 7 mins to fall asleep, lasts 5-10 mins
  - About 5% of our time asleep

Normal Sleep

- **Stage 2**
  - Unconscious, but awakened easily
  - Heart rate and temp begin to drop
  - No eye movements
  - Theta Waves on EEG
  - Lasts about 20 mins
  - About 50% of our time asleep

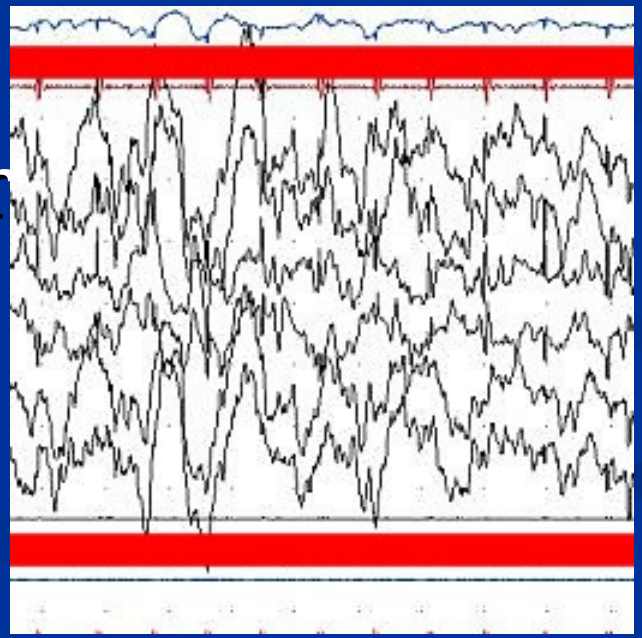
Normal Sleep

- **Stage 3**
  - Transition from light to deep sleep
  - Deep, slow Delta waves emerge
  - 4-6 % of sleep



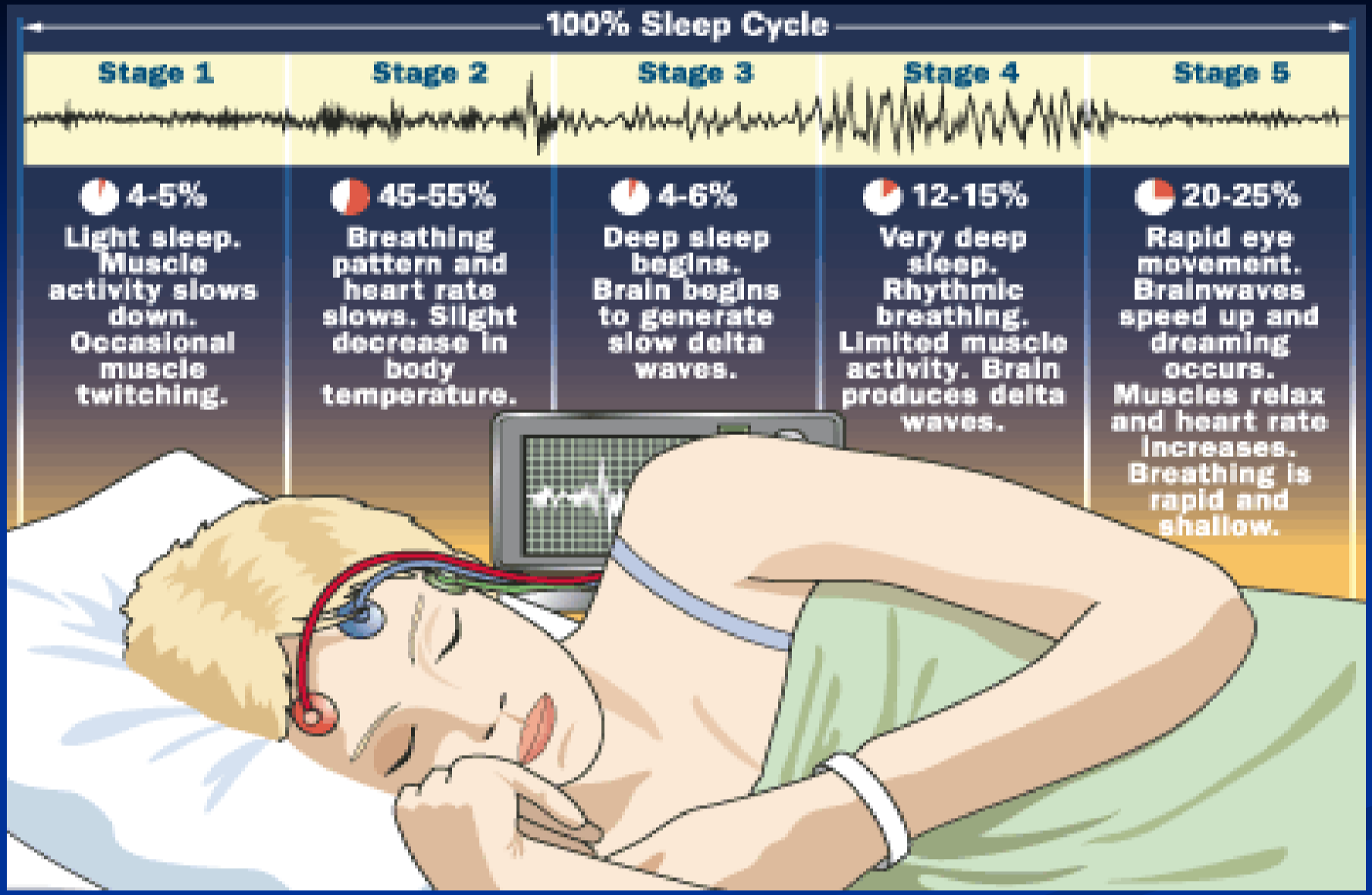
Normal Sleep

- **Stage 4**
  - Deepest stage of sleep
  - Lasts 30 mins
  - May be dreaming
  - Parasomnias occur



Normal Sleep

- **Stage 5**
- **Rapid eye movement (REM) sleep**
  - Paradoxical- brain most active/muscles paralyzed
  - Brain activity most similar to wakefulness
  - Dreaming due to increased brain activity
  - 4 or 5 episodes per night – 20% of total sleep
  - Typically enter REM 90 mins after falling asleep


100% Sleep Cycle
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
4-5%
Light sleep. Muscle activity slows down. Occasional muscle twitching.
45-55%
Breathing pattern and heart rate slows. Slight decrease in body temperature.
4-6%
Deep sleep begins. Brain begins to generate slow delta waves.
12-15%
Very deep sleep. Rhythmic breathing. Limited muscle activity. Brain produces delta waves.
20-25%
Rapid eye movement. Brainwaves speed up and dreaming occurs. Muscles relax and heart rate increases. Breathing is rapid and shallow.

Normal Sleep

- **Cycles**
  - Stages do not progress in sequence:

NREM 1, 2, 3, 4, 3, 2 then REM, back to 2

  - Sleep cycles through these stages 4-5 times nightly
  - Each cycle 90-120 min
  - Each cycle becomes longer
  - Long dreams? REM can last up to 1 hr

Normal Sleep

- **Circadian Rhythm**
  - Natural clock is about 25 hrs
  - Biological clock based on environmental cues

- **Sleep "Requirements":**
  - Infants: 15-16 hours/day
  - Teens: 8-10 hours/day
  - Adults: 6-9 hours/day (including elderly)

Sleep Disorders:

- Insomnia
- Hypersomnolence
- Narcolepsy
- Breathing-related sleep disorder
- Circadian rhythm disorders
- Dyssomnia NOS

Insomnia Disorder

- Difficulty initiating or maintaining sleep OR nonrestorative sleep that lasts for at least one month.
- Objective daytime sleepiness or subjective feeling of not being rested
- No other psych or medical causes
- May not have PSG evidence
- More common in women and elderly
- Prevalence 1-10% (25% in elderly)
- Sleep hygiene
- Sedatives/hypnotics

Hypersomnolence Disorder

- Excessive sleepiness for at least one month i.e., prolonged sleep episodes or naps
- PSG evidence
- Kleine-Levin syndrome
  - Adolescent males
  - Hypersomnia / hyperphagia / hypersexuality

Narcolepsy

- Sleep attacks occur daily ≥ three months
- One or both of the following must be present:
  - Cataplexy: sudden, reversible loss of muscle tone, may be mistaken for seizure,
  - Recurrent intrusions of REM sleep; may include paralysis of voluntary muscles or dreamlike hallucinations
- Tetrad of symptoms (20% have all 4)
  - 1. Sleep paralysis at times of transition to or from sleep
  - 2. Sleep attacks (10-15 min sleep onset REM)
  - 3. Cataplexy
  - 4. Hypnagogic hallucinations

Narcolepsy

- Sleep is generally refreshing
- However, may also suffer from insomnia
- Occurrence: 1: 3000, under- diagnosed
- Equal in men and women
- Generally begins in late teens or early 20s
- Genetic factors, reduced levels of neurons that produce hypocretin, i.e., affects appetite and sleep patterns

Breathing-Related Sleep Disorder

- Sleep disruption, leading to excessive sleepiness or, less commonly, to insomnia, that is judged to be due to abnormalities of ventilation
- Apnea (>10 sec w/ 4% decrease in POx)
- Sleep is not refreshing.

Obstructive Sleep Apnea

- Prevalence: 1-2% in adult male population but 8.5% in those 40-65 y/o, obese and smoking.
- Snoring/choking/enuresis/reflux/cardiac dysrhythmias
- Occlusion of the upper airway (pharynx)
- TX: nCPAP or BiPAP

Circadian Rhythm Sleep-Wake Disorders

- Conflict in circadian rhythm
- Timing of sleep is affected
- Shift-work sleep type, delayed sleep phase type (night owls), advanced sleep phase type (morning larks), irregular sleep-wake type (insomnia/napping), Non 24 hr type
- Sleep phase adjustment / light therapy

Other sleep d/o

- **Restless Leg Syndrome**
  - Deep sensation of creeping or aching inside the legs when lying or sitting producing urge to move them
  - Associated w/ renal failure/diabetes/iron def anemia/ peripheral nerve injury
  - Affects sleep initiation
  - SSRI make it worse
  - Tx: L-dopa, ropinirole, pramipexole, clonazepam, ramelteon, zolpidem, eszopiclone

Parasomnias:

- Undesired activity/behavior during sleep
- Children more often than adults
- Specific sleep stages and during transitions from one stage to the next
- Recall of episode is poor and awakening the individual is difficult
- Examples: Sleepwalking, night terrors, enuresis

Light Sleep Stage Disorders

- **During stages 1 & 2**
- **Bruxism**
  - Tooth grinding
  - Underlying stress or dental condition
  - Side effect of SSRI
  - Mouth guard
- **Sleep talking (somniloquism)**
  - No tx warranted unless related to other psych d/o

NREM Sleep Disorders

- **Stages 3 & 4**
- **Sleepwalking (somnambulism)**
  - During first 3rd of the night and partial emergence from delta sleep
  - Accidents can occur
  - Hard to arouse and amnestic to event
  - Starts in childhood and often resolves by adolescence
  - Prevalence 1-5%, although 10-30% of children will have at least one episode
  - Tx: Safety

NREM Sleep Disorders

- **Night Terrors**
  - Occurs during partial arousal from delta sleep early in the night
  - Patients wake abruptly from sleep screaming and flailing w/ tachypnea, tachycardia and sit up in bed.
  - Last 1-10 min
  - Patients are not alert and are often very difficult to console as well as amnestic to the event
  - In children not usually associated w/ other psych disorders, but in adult can be PTSD
  - Prevalence 1-6% children ages 4-12
  - Tx: reassurance, stress reduction, hypnotics/sedatives, benzos, SSRIs, TCAs.

REM Sleep Disorders

- **Nightmare disorder**
  - Terrifying dreams that are remembered
  - No autonomic arousal
  - Muscle atonia
  - Late in the night
  - The individual becomes fully alert on awakening.
  - Tx: reduce stress, therapy for anxiety, trauma hx
  - Rx: Prazosin, Propranolol

Other Sleep Disorders

- Sleep problems related to:
  - Psychiatric disorders
  - Medical disorders
  - Substance use

Psychiatric Disorders and Sleep

- **Psychotic disorders**
  - Associated problems w/sleep initiation/maintenance
- **Mood disorders**
  - Early morning awakening, decreased delta sleep, decreased REM latency, longer total REM
  - **Atypical depression:** hypersomnia and hyperphagia
  - **Bipolar:** longer total REM during depressed phase and shorter during manic phase
- **Anxiety disorders**
  - Disorder most commonly related to insomnia

Medical Conditions and Insomnia

- The most frequent comorbid c/o
- Tx the underlying medical condition:

Pain

Cluster HA

Metabolic disorders

Asthma

GERD

Infections

Substance/Medication Induced Sleep Disorder

- Generally if the substance is a CNS depressant, withdrawal = insomnia
- If stimulant withdrawal = hypersomnia
- Alcohol
  - Acute intoxication: drowsiness, reduced REM w/ increased stage 3 & 4, fragmentation of the sleep cycle
  - Acute withdrawal: opposite of acute intoxication
  - Chronic use: insomnia, seen commonly post SARP inpatient/dependence, difficult to tx
  - Caution w/ Rx due to relapse potential

Treatments for Insomnia

Cognitive Behavioral Therapy (CBT) for Insomnia

- sleep hygiene education
- stimulus control
- sleep restriction therapy
- addresses dysfunctional beliefs and assumptions about sleep and insomnia.

Sleep Hygiene

- Attempt to maintain regularity in the sleep–wake cycle timing.
- Exercise regularly, but not within a few hours of bedtime.
- Develop a relaxing evening routine.
- Reserve the bedroom and bed for **sleep** and **sex**ual activities.
- Avoid caffeine after lunchtime.
- Avoid alcohol, especially within a few hours of bedtime.
- Avoid late heavy meals, but consider a small bedtime snack.
- Avoid bedroom temperature extremes.
- Avoid disruptive noises and consider a white noise machine.
- Avoid excessive wakeful time in bed.

Medications used to aid sleep

- Benzodiazepines
- Benzodiazepine analogs (Non benzodiazepine GABA A receptor agonists)
- Antihistamines
- Antidepressants
- Herbals
- Antipsychotics
- Mood stabilizers
- Blood pressure medications

Class	Agent	Dose (mg)	Half life (h)	Receptor	Year approved	Side effects	Comments
Benzodiazepine	Flurazepam	15–30	50–100	GABA-BZD	1970	Dizziness, drowsiness, ataxia, amnesia, falls, gastrointestinal upset	FDA approved for insomnia; abuse potential; rebound insomnia; tolerance and dependence; hangover effect; increased fall risk; cytochrome P450 metabolism
	Estazolam	0.5–2	10–24	GABA-BZD	1980		
	Temazepam	7.5–30	8–25	GABA-BZD	1981		
	Triazolam	0.125–0.25	1.5–5.5	GABA-BZD	1982		
	Quazepam	7.5–15	39–73	GABA-BZD	1985		
Sedative-Hypnotics	Zolpidem	5–20	2.5–2.8	GABA-A: alpha-1	1993	Dizziness, drowsiness, amnesia, headache, gastrointestinal upset	For sleep-onset insomnia; risk of dependence & rebound; abuse potential
	Zaleplon	5–10	1.0	GABA-A: omega 1	1997	Headache, dizziness, myalgia, amnesia	For sleep-onset insomnia; no tolerance or hangover
	Eszopiclone	1–3	5–7	GABA-A	2004	Dry mouth, unpleasant taste, dizziness, amnesia, gastrointestinal upset	Studied in elderly; favorable side-effect profile; FDA approved for long-term use
Melatonin receptor agonist	Ramelteon	8	1.5	MT1, MT2	2005	Fatigue, dizziness, headache, nausea	Studied in elderly; favorable side-effect profile
Antidepressants	Trazodone	50–150	Early: 3–6 Late: 5–9	Possible: 5-HT2	1981	Antidepressant, dry mouth, dizziness, headache, nervousness, orthostasis	Not FDA approved for insomnia; primary use: depression
	Amitriptyline	10–100	12–24	5-HT2 noradrenaline	1961	Dry mouth, dizziness, QTc prolongation, constipation, orthostasis	Not FDA approved for insomnia; narrow therapeutic window; anticholinergic side-effects; cardiotoxic; overdose potential
	Doxepin	75–150	Early: 17 Late: 52	Postsynaptic: H1, H2, Alpha-1, 5-HT2, muscarinic	1969		
	Trimipramine	25–100	11–23	Postsynaptic: H1, H2, Alpha-1, 5-HT2, muscarinic	1982		
Nonpresecription	Diphenhydramine	25–50	2–9	Antihistamine: H-1	1946	Drowsiness, dry mouth, dizziness, constipation	Not FDA approved for insomnia; anticholinergic side-effects
	Melatonin	1–3	1–2	Melatonin		Headache,	No quality controls;

Benzodiazepines

Drug	*Daily dosage (mg)*	*Peak action (hours)*	*Half-life (hours)*	*Cost, 30 days (generic)**	*Adverse effects and considerations*	*FDA approved?*
Triazolam (Halcion)	0.125 to 0.5	1 to 2	1.5 to 5	$42 (18 to 21)	Rapid onset, short half-life; anterograde amnesia, rapid eye movement sleep rebound; CYP3A4-dependent metabolism	Yes
Estazolam (ProSom)	1 to 2	2 (0.5 to 6)	10 to 24	43 (18 to 27) for 1 mg nightly	Rapid onset, intermediate half-life; daytime sleepiness	Yes
Temazepam‖ (Restoril)	7.5 to 30	1.2 to 1.6	3.5 to 18.4	99 (20 to 21) for 15 mg	Medium onset, intermediate half-life; daytime sleepiness, less effective sleep induction	Yes

Nonbenzodiazepines

Drug	Daily dosage (mg)	Peak action (hours)	Half-life (hours)	Cost, 30 days (generic)*	Adverse effects and considerations	FDA approved?
Zolpidem (Ambien)	5 to 10	0.5	2 to 3	$102	Abdominal pain, rebound insomnia; controlled-release formulation better for sleep maintenance; FDA pregnancy risk category B (not controlled-release formulation); CYP3A4-dependent metabolism	Yes
Zaleplon (Sonata)	5 to 10	0.5	1	103	Better for sleep maintenance; altered color perception; CYP3A4-dependent metabolism	Yes
Eszopiclone (Lunesta)	2 to 3	1	4 to 6	121	Unpleasant taste (8 to 24 percent), amnesia, hallucinations, worsening depression; CYP3A4-dependent metabolism	Yes

Antihistamines

Drug	Daily dosage (mg)	Peak action (hours)	Half-life (hours)	Cost, 30 days (generic)*	Adverse effects and considerations	FDA approved?
Diphenhydramine (Benadryl)	25 to 50	1 to 3	8	5 (1 to 3)	Anticholinergic,‡ CNS depression/stimulation; FDA pregnancy risk category B	Yes
Doxylamine (Unisom)	12.5 to 25	2 to 3	10	8	Anticholinergic, CNS depression/stimulation; FDA pregnancy risk category A	Yes
Hydroxyzine (Vistaril)	25 to 100	2	3 to 7	37 (9 to 21)	Anticholinergic, CNS depression/stimulation	No

Antidepressants

Drug	Daily dosage (mg)	Peak action (hours)	Half-life (hours)	Cost, 30 days (generic)*	Adverse effects and considerations	FDA approved?
Amitriptyline	25 to 100	2 to 4	17 to 40	21 (2 to 4)	Anticholinergic, morning sedation, daytime somnolence, accidents, cardiac toxicity, sexual dysfunction, serotonin syndrome (SSRI interaction), exacerbates restless legs syndrome and periodic limb movement; CYP2D6-dependent metabolism	No
Trazodone (Desyrel)	50 to 150	0.5 to 2	8	68 (9 to 13)	Same as above	No
Mirtazapine (Remeron)	15 to 45	1.2 to 1.6	20 to 40	104 (81 to 83)	Anticholinergic, dyspnea, edema, hyper- or hypokinesia, increased appetite Rare: facial edema, delusions, hallucinations, seizures, abdominal pain, back pain, agranulocytosis	No

Herbals

Drug	Daily dosage (mg)	Peak action (hours)	Half-life (hours)	Cost, 30 days (generic)*	Adverse effects and considerations	FDA approved?
Melatonin	0.5 to 10	1	0.5 to 2	3 to 5 for 3 mg	Sleep disruption, daytime fatigue, headache, dizziness, irritability	No
Valerian root	200 to 1,000	1	Not known	2 to 3 for 450 mg	Daytime sedation, hepatotoxicity	No

Prescribing Sedative-Hypnotics

- **All FDA-approved hypnotic medications share class-label prescribing guidelines.**
  - indicated for short-term use.
  - long-term use is not restricted.
  - no more than 30 pills being prescribed at one time
- 10% to 15% of patients who are prescribed hypnotics use them chronically.

Benzodiazepine Info

- **Contraindicated**
  - narrow-angle glaucoma
  - untreated obstructive sleep apnea
  - history of substance abuse

Benzodiazepine Info

- Adverse effects:
  - Drowsiness
  - Dizziness
  - risk of falls and motor vehicle collisions
  - cognitive and functional decline
  - fatal overdose
  - Tolerance
  - rebound insomnia
- Reduce dosage in older adults; use caution with narcotics
- additive effects with alcohol and CNS depressants.
- **Up to 30 percent of chronic benzodiazepine users develop dependence**.

Zolpidem (Ambien

- decreases sleep-onset latency, improves sleep quality, increases stage 2 and slow-wave sleep
- does not exhibit tolerance or rebound following five weeks of continuous use at recommended dosages.
- Adverse effects occur at daily dosages of 20 mg or more.
- Should not be readministered following nocturnal awakenings
- a controlled-release version (Ambien CR) in a dosage of 6.25 to 12.5 mg daily may be better for maintaining sleep
  - has not been shown to reduce adverse effects.

Zaleplon (Sonata

- decreases sleep-onset latency
- short half-life - 1 hour
- enables readministration following nocturnal awakenings.
- useful in patients who have trouble falling asleep and maintaining sleep
  - can be administered up to four hours before the anticipated wake time
- causes less memory and psychomotor impairment than do benzodiazepines and zolpidem.
- Some report visual disturbances, such as a change in color perception.
- The onset of action may be delayed if taken with a high-fat meal.

Eszopiclone (Lune

- only hypnotic with FDA approval for use longer than 35 days.
- evidence of effectiveness for six months of therapy in a randomized, placebo-controlled trial, although there is some attenuation of its effect over time.
  - significant and sustained decreases in sleep-onset latency, wake time, number of awakenings, and number of nights awakened per week
  - it also improves total sleep time and quality of sleep.
- Higher doses (2 to 3 mg) are more effective for sleep maintenance.
- Lower doses (1 to 2 mg) are suitable for difficulty in falling asleep.
- The onset of action may be delayed if taken with a high-fat meal.
- Rare cases of fatal overdose when used with other CNS depressants have been reported.

Ramelteon (Rozere

- **Selective Melatonin Receptor Agonist**
  - targeting the melatonin receptors in the brain.
  - reduces sleep-onset latency and increases sleep periods
  - Can be taken long-term and daily
- patient evaluations of improvement are inconsistent and there are no comparison studies.
  - not been studied in patients with depression, anxiety, shift work, or jet lag.
- There is a low likelihood of abuse and physical dependence.
- Serious adverse effects are rare
  - less than 1 percent of patients.
- Common side effects
  - somnolence, headache, fatigue, nausea, and dizziness.
- hepatic metabolism
- Ramelteon is the only nonscheduled drug for insomnia.

Trazodone (Desyr

- Serotonin reuptake inhibitor, but at lower doses antagonize serotonin
- All of the antidepressants except trazodone suppress REM sleep
- Mechanisms of sedative effect of antidepressants: histamine (H 1), serotonin type 2 (5HT2) receptor antagonism, and possibly alpha1-adrenergic receptor antagonism
- Rare priapism in men and clitoral engorgement in women
- Consider contribution to serotonin syndrome

Antihistamines

- Nearly 25 percent of patients with insomnia use over-the-counter (OTC) sleep aids.
- 5 percent use them at least several nights a week.
- Chronic use of OTC antihistamines such as diphenhydramine (Benadryl) and doxylamine (Unisom) should be discouraged
  - decreased REM sleep
  - anticholinergic: dry mouth, urinary retention, decrease cog function, intraocular pressure
  - can cause residual drowsiness

Prazosin (Minipress)

- Alpha 1 adrenergic antagonist
- Data support the efficacy of prazosin for nightmares, sleep disturbance, and other PTSD symptoms
- mean dose=9.5 mg/day at bedtime, SD=0.5
- Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. - Raskind MA - *Am J Psychiatry* - 01-FEB-2003
- Not FDA approved

Secondary options/comorbid conditions

- Beta- blockers: Propranolol /HTN
- Antihypertensives: Clonidine /ADHD/anxiety
- Tricyclics: Doxepin /mood/pain
- Anticonvulsants: Gabapentin, Pregabalin/ h/a, pain, fibromyalgia, neuropathy
- Atypical Antipsychotics: Risperdal, Seroquel/ psychosis, mania, impulse control, anxiety

Opiates

- Fragments sleep
- Decrease REM and stage 2 sleep
- May be appropriate in carefully selected patients with temporary pain-associated insomnia.
- Dependence

Alcohol

- At least 10 percent of young adults use OTC medications or alcohol in any given year to improve sleep.
- Acts directly on GABA-gated channels reducing sleep-onset latency
- Increases wakefulness after sleep onset
- Suppresses rapid eye movement (REM) sleep.
- Alcohol has the potential for abuse and should not be used as a sleep aid, i.e., Nyquil

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